(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 710 122 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
12.12.2001 Bulletin 2001/50

(21) Application number: **94920617.1**

(22) Date of filing: **22.06.1994**

(51) Int Cl.[7]: **A61K 47/18**, A61K 38/11

(86) International application number:
PCT/SE94/00622

(87) International publication number:
WO 95/01185 (12.01.1995 Gazette 1995/03)

(54) STABILIZED PHARMACEUTICAL PEPTIDE COMPOSITIONS

STABILISIERTE PHARMAZEUTISCHE PEPTIDPRÄPARATE

COMPOSITIONS PHARMACEUTIQUES PEPTIDIQUES STABILISEES

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

(30) Priority: **29.06.1993 US 84563**

(43) Date of publication of application:
08.05.1996 Bulletin 1996/19

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Printed by Jouve, 75001 PARIS (FR)

EP 0 710 122 B1

Description

[0001] The present invention relates to a stable, aqueous composition for administration to a patient of at least one biologically active peptide. Furthermore the invention relates to an aqueous composition for nasal administration. The present invention especially relates to stabilized aqueous pharmaceutical compositions for nasal, oral or parenteral administration of small and medium-size peptides (up to about eicosapeptides), such as desmopressin (1-deamino-8-D-arginine vasopressin; DDAVP).

[0002] As used herein, the term "stabilized composition" refers to an aqueous solution for therapeutic use, containing at least one small or medium-size biologically active peptide. Such stabilization should allow the composition to be stored at room temperature for extended periods without loss in biological activity.

[0003] A substantial number of biologically active peptides, their derivatives and analogs (in the following termed "peptides") are known to be therapeutically useful. For various reasons they are often administered in form of aqueous compositions, that is, sterile aqueous solutions containing a known amount of peptide.

[0004] The biological activity of the peptides to be administered is often extremely high. Thus, only very small amounts of peptide are needed for a single dose. Such dilute peptide solutions in general are not stable at room temperature for longer periods, even if kept in sealed containers. The therapeutically active peptide hormone analog desmospressin is such a peptide. Its aqueous solution has to be stored at a temperature not exceeding 8°C. Storage at higher temperatures such as, for instance, room temperature, results in the degradation of desmopressin by hydrolytic and/or oxidative processes which are not blocked by the addition of a preservative, such as chlorobutanol (1,1,1-trichloro-2-methylpropan-2-ol). However, chlorobutanol effectively protects desmopressin against microbial attack.

[0005] Another problem with dilute aqueous solutions of peptides is the adsorption of minute amounts of peptide to the walls of the container in which the solution is kept. Since such peptide solutions are usually very dilute, adsorption of even minor amounts may substantially reduce the amount of peptide available for administration. EP 0 199 992 for example refers to an adsorption-resistant peptide composition containing benzalkonium chloride and/or bezethonium chloride to prevent the peptide from being adsorbed on the inner wall of a container or equipment. But this peptide solutions are not stable at room temperature or at higher temperatures for longer periods.

[0006] A particularly attractive way of administration of small and medium-size peptides in solutions is via the nasal mucosa, either as drops or in spray form, which is even more convenient and more reproducible. Desmopressin, for instance, can be administered in an aqueous, 0,9% sodium chloride solution (saline) by this route.

[0007] Various kinds of intranasal spray delivery devices are known in the art. In general, peptides in an aqueous solution are administered by means of metered-dose spray pumps, such as those manufactured by Ing. Erich Pfeiffer KG, Radolfzell, Germany. An alternate route is via a graduated plastic tube of special design called "rhinyle" which is partially filled with an aqueous solution containing a peptide. One end of the rhinyle is placed in the mouth and the other end is placed in the desired nostril. The solution is then delivered to the nostril by blowing.

[0008] Peptides for nasal administration often have extremely high biological activity, and only a very small amount of peptide is needed in a single dose. However, the particular form of administration may require a minimum liquid volume for good reproducibility. Thus, effective concentration ranges for nasally administered peptides are generally quite low. For instance, a single desmopressin dose for nasal administration is typically between 10 µg to 40 µg, but may even be as little as 2.5 µg and as high as 300 µg. Typical dose volumes are from 100 µl to 400 µl (4 x 100 µl). These doses are normally taken on a regular basis, such as at least once daily.

[0009] Thus, it is an object of the present invention to overcome the aforementioned stability and storage problems associated with known aqueous solutions of small and medium-size peptides, particularly of aqueous solutions containing desmopressin.

[0010] Another object is to provide a stabilized aqueous solution containing a peptide for nasal, oral or parenteral administration which can be conveniently stored at room temperature for extended periods of time, for instance, one year, without risking partial or total degradation or microbial contamination of the peptide contained therein.

[0011] A further object is to protect the peptide in solution from adhering to the walls of the container without using extraneous additives specifically designed for that purpose.

[0012] Yet another object is to provide an aqueous nasal or drop spray composition for the management of diseases and abnormal conditions which are mitigrated by administration of small and medium-sized biologically active peptides.

[0013] The above mentioned problems are solved by a stable aqueous composition for administration to a patient according to claim 1. Furthermore these problems are solved by an aqueous composition for nasal administration according to claim 8 and by a stable aqueous composition for nasal application according to claim 13. - The present invention is an aqueous composition for administration of small and medium-size peptides, particularly desmopressin, which can maintain stability over time and at room temperature, of active biological ingredients carried therein such as a peptide, an analog of a peptide or mixtures of peptides and/or their analogs. The solution contains a buffer, benzalkonium chloride and an osmotic pressure-controlling agent.

[0014] The benzalkonium chloride selectively used have, in addition to its namesake functions, the unexpected ability

to prevent adsorption of small and medium-size peptide components from adhering to container walls, particularly walls of containers made of polymeric materials.

[0015] It is preferred for the peptide or peptide analog to be oxytocin or vasopressin, or their analogs and derivatives, such as particularly preferred, desmopressin (hereinafter also "DDAVP"). According to the invention the peptide or peptide analog can be terlipressin ((N- -triglycyl-8-lysine)-vasopressin), atosiban ((Mpa^1, D-Tyr(Et)^2, Thr^4, Orn^8)-oxytocin), carbetocin ((1-desamino-1-monocarba-2(O-methyl)-tyrosine)oxytocin or triptorelin [D-Trp^6]-LHRH, or their analogs and derivatives.

[0016] It is preferred for the buffer to be capable of maintaining a pH of about 5.0.

[0017] According to the invention the stabilized peptide solution contains citrate and/or phosphate. Preferred buffer systems according to the invention are citric acid/disodium hydrogen phosphate, sodium dihydrogen phosphate/disodium hydrogen phosphate, and citric acid/sodium citrate. Specifically preferred is a buffer comprising: citrate - phosphate - sodium ions in a molar ratio of from about 1 : 3 : 3 to about 1 : 1 : 2.

[0018] The aqueous composition according to the invention contains benzalkonium chloride, $(NR^1R^2R^3R^4)^+Cl^-$; where R^1, R^2 = methyl, R^3 = benzyl, R^4 = C_8H_{17} to $C_{18}H_{37}$. The composition according to the invention preferably contains the bezalkonium chloride in a concentration from about 0.05 to about 0.2 mg per ml. Particularly preferred is a concentration of about 0.1 mg per ml.

[0019] It is preferred for the osmotic pressure-controlling agent to be sodium chloride. The buffer components also contribute substantially to osmotic pressure control.

[0020] According to a preferred aspect of the invention the composition additionally contains at least one mucosal absorption enhancer such as bile salts, monolauryl ethers of macrogols, phospholipids, and fusidate derivatives.

[0021] A preferred embodiment of the composition according to the invention contains from 0.025 mg to 1.5 mg of desmopressin acetate, from 1.35 to 1.75 mg of citric acid, from 2.25 to 2.65 mg of disodium hydrogen phospate, from 0.05 to 0.20 mg bezalkonium chloride, and sodium chloride in an amount sufficient to provide the overall solution with an asmotic pressure comparable to that of human plasma.

[0022] The invention furthermore refers to a sealed container filled with an stabilized aqueous spray composition for nasal administration of said desmopressin according to claim 14. The aqueous spray composition can be used for the management of diseases and abnormal conditions that can be treated by nasal administration of small and medium-size peptides.

[0023] FIGURE 1 graphocally illustrates the results of stability testing for the compositions prepared according to the present invention.

[0024] The invention will now be explained in more detail by reference to the following experimental examples:

Example 1

[0025] Preparation of test compositions. Five test compositions containing desmopressin (DDAVP) acetate for nasal spray or drop compositions containing various preservatives were prepared, compositions A, B, C, D and E (see Table 1). Each test sample contained 0.089 mg DDAVP free base per ml, and Table 1 denotes the type of buffer used in each system. Millipore® -filtered water was used as solvent.

[0026] Compositions A and B were prepared according to the present disclosure. Compositions C, D and E were prepared for comparative testing of other preservatives.

[0027] The stability of the known, unbuffered Minirin® (DDAVP) spray containing NaCl and chlorobutanol has a useful shelf life of 3 years at refrigerated storage when kept in sealed glass containers. It is not stable at room temperature when stored for longer periods of time. Note that composition E contains NaCl and chlorobutanol, but is a buffered solution.

Table 1

Stabilized desmopressin compositions (amounts per ml)				
A and B denote compositions according to the invention; C, D, E denote compositions prepared for comparison				
Composition	NaCl mg	BH mg (mmol)	B^-Na^+ mg	Preservative mg
A	8.74	AcOH (mmol) $2.96 \cdot 10^{-3}$	NaOAc 0.58	benzalkonium chloride, 0.1
B	6.29	citric acid 1.56	Na_2HPO_4 2.43	benzalkonium chloride, 0.1

Table 1 (continued)

Stabilized desmopressin compositions (amounts per ml)				
A and B denote compositions according to the invention; C, D, E denote compositions prepared for comparison				
Composition	NaCl mg	BH mg (mmol)	B^-Na^+ mg	Preservative mg
C	5.24	citric acid 1.97	Na_2HPO_4 1.83	benzyl alcohol 10.0
D	6.30	citric acid 1.56	Na_2HPO_4 2.43	methyl p-hydroxy benzoate*, 0.80 propyl p-hydroxybenzoate**, 0.20
E	5.64	citric acid 1.97	Na_2HPO_4 1.83	chlorobutanol 5.00

*methyl paraben;
**propyl paraben

Example 2

[0028] Stability testing by detecting peptide degradation. The DDAVP-compositions prepared in Example 1 were stored in 10 ml glass vials (hydrolytic class 1, provided with Teflon® stoppers) in the dark at 65° C for up for 13 weeks. Samples were taken after 1, 2, 3, 5, 7, 9, 11, and 13 weeks and analyzed for DDAVP by HPLC [Varian Star system; Lichrospher® PR-18 5µm column (50 x 4 mm); gradient elution with various proportions of acetonitrile/0.0667 M aqueous phosphate buffer pH 7].

[0029] The results are graphically depicted in Fig. 1 and demonstrate the superior stabilizing effect of the composition according to the invention. The experimental data contained in Fig. 1 were also used for calculation of first order rate constants shown in Table 2, below.

Table 2

First order rate constants for degradation ot desmopressin		
Composition	k (s^{-1})	correlation coefficient
A	$4.6 \cdot 10^{-8}$	0.98
B	$8.0 \cdot 10^{-8}$	0.98
C	$1.6 \cdot 10^{-7}$	0.97
D	$8.8 \cdot 10^{-8}$	0.96
E	$\sim 9 \cdot 10^{-7}$	0.83

Example 3

[0030] Calculation of useful shelf-life. From the slopes of the curves in Fig. 1 and from corresponding storage tests carried out at 37° C, 50° C, and 60° C Arrhenius activation energies (E_a) were obtained for compositions A, B, C and D. Composition E did not show Arrhenius-type behaviour since it was the least stable composition by far.

[0031] The storage time over which total DDAVP content of each composition was reduced by 10% (t_{90}) at 25° C and 30° C, "useful shelf life", was calculated from E_a which is tabulated below in Table 3.

Table 3

Useful shelf life in years (t_{90}) for stabilized desmopressin compositions			
Composition	activation energy	t_{90}	
	(E_a, kJ/mol)	25° C	30° C
A	123.5	27.0	11.9
B	115.1	12.9	6.0
C	115.5	5.7	2.7
D	102.8	7.4	3.7

[0032] As Table 3 shows, desmopressin is preserved in compositions A and B for extended periods of time at room temperature, thus demonstrating the ability of the present invention to be stored and used for extensive periods without refrigeration.

Example 4

[0033] **Comparison of intra-nasal desmopressin uptake.** 24 healthy fasting male subjects were given (randomized) desmopressin (20 µl) intransally in spray form (200 µl), using either compositon B or the commercially available unbuffered Minirin® formulation containing chlorobutanol as preservative. Blood samples were collected at intervals and desmopressin plasma levels monitored over a 12 h period by a desmopressin-specific RIA plasma assay (Lundin, S. et al., Acta Endocrinologica (Copenhagen) **108** (1985) 170-183). Essentially the same desmopressin plasma level profile was found for the two compositions. This is an unexpected result since H.A. Batts et al. (J. Pharm. Pharmacol. **1989**, 156-159) found that chlorobutanol and benzalkonium chloride differed significantly in their effect on the mucociliary transport rate in a frog palate model. The rate of mucociliary clearance affects the comparatively slow intra-nasal uptake of peptides and other nasally administered biologically active compounds.

Example 5

[0034] **Absorption-blocking effect of desmopressin.** Sterile aqueous solutions of desmopressin marked with ^{125}I (appr. 10,000 CPM/ml) containing benzalkonium chloride + saline, chlorobutanol + saline, or saline only, were all incubated in tubes of polystyrene, polypropene and glass for 24 h at ambient temperature.

[0035] In the solutions containing benzalkonium chloride and chlorobutanol, respectively, desmopressin showed insignificant adsorption, whereas only about half of the amount of desmopressin in the preservative-free solution could be recovered from the plastic tubes.

[0036] While the various features and embodiments of the present invention have been described herein, it is possible that one skilled in the art could modify the various aspects of the invention and obtain the same objectives. The present disclosure contemplates such modifications as being within its spirit and scope.

Claims

1. A stable, aqueous composition for administration to a patient of at least one biologically active peptide selected from the group consisting of oxytocin, vasopressin, terlipressin, atosiban, carbetocin and triptorelin, and analogs and derivatives thereof, comprising:

   a) said biologically active peptide;
   b) a buffer selected from the group consisting of citrate, phosphate and a mixture of citrate and phosphate maintaining the pH of said composition between 4.0 and 6.0,
   c) benzalkonium chloride,
   d) an osmotic pressure-controlling agent.

2. The composition according to claim 1, wherein said buffer maintains said pH at about 5.0.

3. The composition according to claim 1 or 2, wherein said buffer mixture of citrate and phosphate contains sodium ions such that the molar ratio of citrate, phosphate and sodium ions is from about 1 : 3 : 3 to about 1 : 1 : 2.

4. The composition according any of claims 1 - 3, wherein said osmotic pressure-controlling agent is sodium chloride.

5. The composition according to claim 1, wherein said administration is oral.

6. The composition according to claim 1, wherein said administration is parenteral.

7. The composition according to any of claims 1 - 6, wherein said peptide is desmopressin.

8. An aqueous composition for nasal administration of at least one biologically active peptide selected from the group consisting of oxytocin, vasopressin, terlipressin, atosiban, carbetocin and triptorelin, and analogs and derivatives thereof, comprising:

a) said biologically active peptide,
b) a buffer selected from the group consisting of citrate, phosphate and a mixture of citrate and phosphate maintaining the pH of said composition between 4.0 and 6.0,
c) benzalkonium chloride, and
d) an osmotic pressure-controlling agent such that said composition is capable of maintaining said biologically active peptide in a functionally stable condition over extended periods and at room temperature.

9. The composition of claim 8, wherein said peptide is desmopressin.

10. The composition of claim 8 or 9, wherein said buffer maintains said pH at about 5.0.

11. The composition of any of claims 8 - 10, wherein said buffer comprises a mixture of citrate and disodium hydrogen phosphate such that the molar ratio of citrate, phosphate and sodium ions is from about 1 : 3 : 3 to about 1 : 1 : 2.

12. The composition of any of claims 8 - 11, wherein said osmotic pressure-controlling agent is sodium chloride, said sodium chloride being added to said composition in an amount sufficient to make said composition compatible with the osmotic pressure of human plasma.

13. A stable aqueous composition for nasal application, comprising:

a) from 0.025 mg to 1.5 mg of desmopressin acetate;
b) from 1.35 mg to 1.75 mg of citric acid;
c) from 2.25 mg to 2.65 mg of disodium hydrogen phosphate;
d) from 0.05 mg to 0.20 mg of benzalkonium chloride; and
e) sodium chloride in an amount sufficient to provide said composition with an osmotic pressure comparable to that of human plasma.

14. A sealed container filled with a stabilized aqueous spray composition according to claim 13 for nasal administration of said desmopressin.

Patentansprüche

1. Stabile wässrige Zusammensetzung zur Verabreichung, einem Patienten, mindestens eines biologisch aktiven Peptids, das aus der von Oxytocin, Vasopressin, Terlipressin, Atosiban, Carbetocin und Triptorelin sowie Analogen und Derivaten davon gebildeten Gruppe ausgewählt ist, umfassend:

a) das genannte biologisch aktive Peptid;
b) einen aus der von Citrat, Phosphat und einem Gemisch von Citrat und Phosphat gebildeten Gruppe ausgewählten, den pH-Wert der genannten Zusammensetzung zwischen 4,0 und 6,0 haltenden Puffer;
c) Benzalkoniumchlorid;
d) ein den osmotischen Druck einstellendes Agens.

2. Zusammensetzung nach Anspruch 1, bei welcher der genannte Puffer den pH-Wert auf etwa 5,0 hält.

3. Zusammensetzung nach Anspruch 1 oder 2, bei welcher das genannte Puffergemisch von Citrat und Phosphat Natriumionen enthält, derart, dass das Molverhältnis von Citrat, Phosphat und Natriumionen von etwa 1 : 3 : 3 bis etwa 1 : 1 : 2 beträgt.

4. Zusammensetzung nach einem der Ansprüche 1 bis 3, bei welcher das genannte den osmotischen Druck einstellende Agens Natriumchlorid ist.

5. Zusammensetzung nach Anspruch 1, bei welcher die genannte Verabreichung oral ist.

6. Zusammensetzung nach Anspruch 1, bei welcher die genannte Verabreichung parenteral ist.

7. Zusammensetzung nach einem der Ansprüche 1 bis 6, bei welcher das genannte Peptid Desmopressin ist.

8. Wässrige Zusammensetzung zur nasalen Verabreichung, einem Patienten, mindestens eines biologisch aktiven Peptids, das aus der von Oxytocin, Vasopressin, Terlipressin, Atosiban, Carbetocin und Triptorelin sowie Analogen und Derivaten davon gebildeten Gruppe ausgewählt ist, umfassend:

   a) das genannte biologisch aktive Peptid;
   b) einen aus der von Citrat, Phosphat und einem Gemisch von Citrat und Phosphat gebildeten Gruppe ausgewählten, den pH-Wert der genannten Zusammensetzung zwischen 4,0 und 6,0 haltenden Puffer;
   c) Benzalkoniumchlorid; und
   d) ein den osmotischen Druck einstellendes Agens, derart, dass die genannte Zusammensetzung fähig ist, über längere Zeiten und bei Raumtemperatur das genannte biologisch aktive Peptid in einem funktionell stabilen Zustand zu halten.

9. Zusammensetzung nach Anspruch 8, bei welcher das genannte Peptid Desmopressin ist.

10. Zusammensetzung nach Anspruch 8 oder 9, bei welcher der genannte Puffer den pH-Wert auf etwa 5,0 hält.

11. Zusammensetzung nach einem der Ansprüche 8 bis 10, bei welcher der genannte Puffer ein Gemisch von Citrat und Dinatriumhydrogenphosphat enthält, derart, dass das Molverhältnis von Citrat, Phosphat und Natriumionen von etwa 1 : 3 : 3 bis etwa 1 : 1 : 2 beträgt.

12. Zusammensetzung nach einem der Ansprüche 8 bis 11, bei welcher das genannte den osmotischen Druck einstellende Agens Natriumchlorid ist, wobei das genannte Natriumchlorid der genannten Zusammensetzung in einer Menge zugegeben wird, die genügt, um die genannte Zusammensetzung mit dem osmotischen Druck von humanem Plasma verträglich zu machen.

13. Stabile wässrige Zusammensetzung zur nasalen Verabreichung, umfassend:

   a) von 0,025 mg bis 1,5 mg Desmopressinacetat;
   b) von 1,35 mg bis 1,75 mg Citronensäure;
   c) von 2,25 mg bis 2,65 mg Dinatriumhydrogenphosphat;
   d) von 0,05 mg bis 0,20 mg Benzalkoniumchlorid; und
   e) Natriumchlorid in einer Menge, die genügt, um der genannten Zusammensetzung einen osmotischen Druck zu verleihen, der demjenigen von humanem Plasma vergleichbar ist.

14. Versiegelter Behälter, der mit einer stabilisierten wässrigen Sprühzusammensetzung nach Anspruch 13 zur nasalen Verabreichung des genannten Desmopressins gefüllt ist.

Revendications

1. Une composition aqueuse stable pour administration à un patient, d'au moins un peptide actif biologiquement, sélectionné dans le groupe composé de l'ocytocine, vasopressine, terlipressine, atosibane, carbétocine et triptoréline et analogues, et leurs dérivés, comprenant :

   a) ledit peptide actif biologiquement ;
   b) un tampon, sélectionné dans le groupe composé des citrate, phosphate et d'un mélange de citrate et de phosphate, maintenant le pH de ladite composition à une valeur comprise entre 4,0 et 6,0,
   c) du chlorure de benzalkonium,
   d) un agent de contrôle de la pression osmotique.

2. La composition selon la revendication 1, dans laquelle ledit tampon maintient ledit pH à une valeur d'environ 5,0.

3. La composition selon la revendication 1 ou 2, dans laquelle ledit mélange de tampon de citrate et de phosphate contient des ions sodium, de manière que le rapport molaire entre les ions citrate, phosphate et sodium soit d'environ 1 : 3 : 3 à environ 1 : 1 : 2.

4. La composition selon l'une quelconque des revendications 1 à 3, dans laquelle ledit agent de contrôle de la pression osmotique est du chlorure de sodium.

5. La composition selon la revendication 1, dans laquelle ladite administration se fait par voie orale.

6. La composition selon la revendication 1, dans laquelle ladite administration se fait par voie parentérale.

7. La composition selon l'une quelconque des revendications 1 - 6, dans laquelle ledit peptide est la desmopressine.

8. Une composition aqueuse pour administration nasale d'au moins un peptide actif biologiquement, sélectionné dans le groupe constitué de l'ocytocine, vasopressine, terlipressine, atosibane, carbétocine et triptoréline et analogues, et leurs dérivées, comprenant :

   a) ledit peptide biologiquement actif,
   b) un tampon sélectionné dans le groupe contitué des citrate, phosphate et d'un mélange de citrate et de phosphate, maintenant le pH de ladite composition dans une plage comprise entre 4,0 et 6,0,
   c) du chlorure de benzalkonium, et
   d) un agent de contrôle de la pression osmotique, de manière que ladite composition soit en mesure de maintenir ledit peptide biologiquement actif en un état fonctionnellement stable sur des périodes étendues et à la température ambiante.

9. La composition selon la revendication 8, dans laquelle ledit peptide est la desmopressine.

10. La composition selon la revendication 8 ou 9, dans laquelle ledit tampon maintient ledit pH à une valeur d'environ 5,0.

11. La composition selon l'une quelconque des revendications 8 à 10, dans laquelle ledit tampon comprend un mélange de citrate et de phosphate disodique hydrogéné, de manière que le rapport molaire entre les ions citrate, phosphate et sodium soit d'environ 1 : 3 : 3 à environ 1 : 1 : 2

12. La composition selon l'une quelconque des revendications 8 à 11, dans laquelle ledit agent de contrôle de la pression osmotique est du chlorure de sodium, ledit chlorure de sodium étant ajouté à ladite composition en une quantité suffisante pour que ladite composition soit compatible avec la pression osmotique du plasma humain.

13. Une composition aqueuse stable pour application nasale, comprenant :

   a) de 0,025 mg à 1,5 mg d'acétate de desmopressine ;
   b) de 1,35 mg à 1,75 mg d'acide citrique ;
   c) de 2,25 mg à 2,65 mg de phosphate disodique hydrogéné
   d) de 0,05 mg à 0,20 mg de chlorure de benzalkonium ; et
   e) du chlorure de sodium en une quantité suffisante pour que ladite composition ait une pression osmotique comparable à celle du plasma humain.

14. Un récipient étanche, rempli d'une composition aqueuse stabilisée à pulvériser, selon la revendication 13, pour administration nasale de ladite desmopressine.

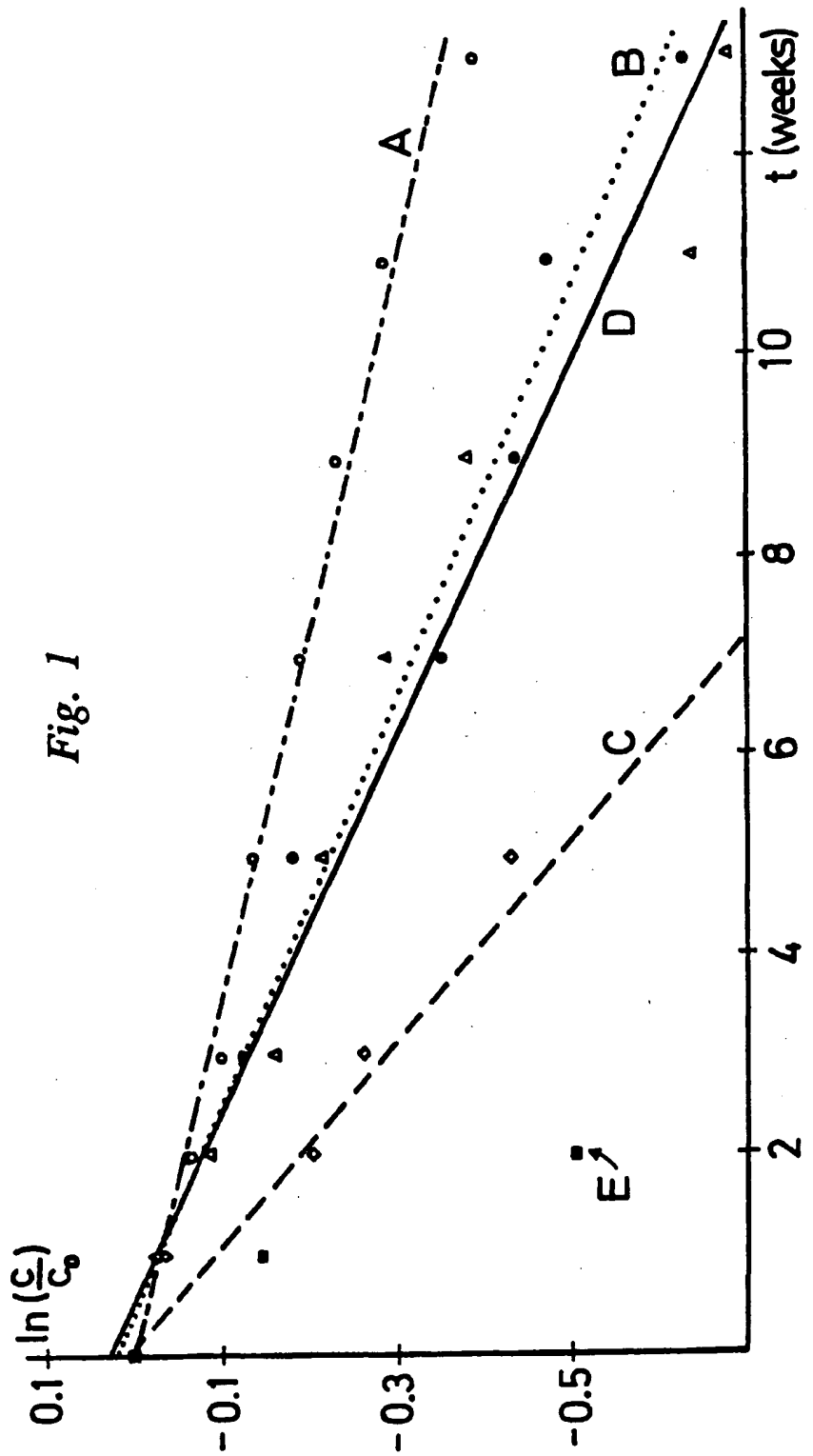

Fig. 1